UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

003066

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

7/8/83

MEMORANDUM

TO: T. A. Gardner, Product Manager #17
Registration Division (TS-767)

THRU: William L. Burnam, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: PP 2E2663, Request for a Tolerance of Deltamethrin (Decamethrin) on Tomatoes (Imported).

TOX Chem. No. 463B

Background:

The American Hoechst Corporation (Somerville, New Jersey) is requesting the establishment of a full tolerance for a residue of,

(S)-α-Cyano-3-phenoxybenzyl (1R, 3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

at 0.05 ppm in or on the raw agricultural commodity tomatoes.

This chemical is known also as deltamethrin, decamethrin, decis and RU-22974.

The tomatoes involved will be grown outside of the United States. No request for registration of a pesticide product containing deltamethrin for use on tomatoes was included with this action.

Several volumes of toxicity data were submitted in support of this petition which included nearly a complete battery of toxicity studies. This is a new chemical and no previous studies have been reviewed by Toxicology Branch.

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RECOMMENDATIONS AND COMMENTS:

1. TOXICOLOGY BRANCH (TB) cannot recommend in favor of this tolerance on tomatoes because RESIDUE CHEMISTRY BRANCH (RCB) has not determined that the tolerance level as proposed (0.05 ppm) is appropriate. See the review by J. Onley dated June 14, 1983. This action will be reconsidered by TB when RCB determines an acceptable tolerance level.

2. A battery of toxicity studies to support the requested tolerance were submitted and reviewed and except for the mouse oncogenicity study were found to be CORE MINIMUM or better when the CORE system was used.

See list of studies reviewed below.

3. The mouse oncogenicity study was reviewed and found to be CORE SUPPLEMENTARY because the highest dose level tested (100 ppm) produced no signs of either systemic toxicity or weight loss. Thus, this study was not conducted at the maximum tolerated dose (MTD) level and in terms of current EPA criteria the study does not fully assess the oncogenic potential of deltamethrin in mice. The study does, however, provide sufficient data to assure TB that deltamethrin does not induce tumors in mice at up to and including 100 ppm by feeding this level in the diet for two years.

The registrant should be advised that future tolerance requests for deltamethrin will be handled on a case by case basis and certain usages may require the completion of a mouse oncogenicity study.

4. Since this proposed tolerance for deltamethrin is for imported tomatoes, no product registration is involved with this action. The data package contained several studies with two formulated products containing deltamethrin and these were reviewed. See the addendum on the toxicity data for the products containing deltamethrin in the last pages of this memo.

5. Some agreement between the importers and the applicators in Mexico (or elsewhere) must be made to assure that only inert ingredients that are cleared for use on crops in the United States will be used on the tomatoes to be imported into this country. Note: TB is aware that the inerts in the product DECIS 2.5 EC are cleared under 40 CFR 180.1001 c,d, or e. Thus, this product may be used on the tomatoes that will be imported into the United States.

6/28/83

John Doherty, Ph.D.
Toxicology Branch
HED (TS-769)

7/8/83

There are no pages 3 and 4. Note - Gadd



Substance Identification (From EPA Acc. No. 070734) 003066

1. Chemical name: (S)-α-cyano-m-phenoxybenzyl (1R,3R)-3-(2,2-dibromovinyl)-2,2-dimethyl cyclopropane carboxylate.

2. Deltamethrin, (preferred name in accordance with IUPAC rules) formerly known as decamethrin, decis, code names RU 22974, NRDC 161, FMC 45498.

3. Purity of technical material > 98.00%. Impurities include [redacted]

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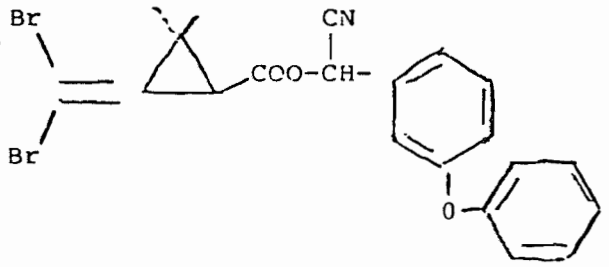
4. Structure:




Molecular Weight 505.2

5. Other physical/chemical properties:

a. Density/sp. Gr.: not given

b. Color/physical state (melting point 98-101°C)

c. Shaughnessey number - (not given)

d. Vapor pressure: $1.5 \times 10^{-8}$ mm Hg at 25°C

e. Solubility: insoluble in water but soluble in organic solvents.

f. Chemical class = synthetic pyrethroid.

IMPURITY INFORMATION IS NOT INCLUDED

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STUDIES REVIEWED AND SYNOPSIS OF TOXICITY
(TECHNICAL MATERIAL)

(See reviews as follows for EPA Acc. No., study date and laboratory.)

| Study | Results | CORE Classification |
|---|---|---|
| Acute Oral-rats ($LD_{50}$) | In polyethylene glycol<br>males: 66.7 (53.0-83.9) mg/kg<br>females: 86.0 (70.6-106.2) mg/kg<br><br>In sesame oil<br>males: 128.5 (104.9-156.5) mg/kg<br>females: 138.7 (114.2-168.2) mg/kg<br><br>(TOX Cat II). | SUPPLEMENTARY<br><br>" |
| Acute dermal-rats ($LD_{50}$) | >2.94 gm/kg | MINIMUM |
| Acute dermal-rabbit ($LD_{50}$) | >2.00 gm/kg (TOX Cat III) | MINIMUM |
| Primary dermal Irritation - rabbits | PII = 0 (TOX Cat IV) | MINIMUM |
| Ocular Irritation rabbits | No corneal involvement (TOX Cat III) | GUIDELINES |
| Acute Inhalation $LC_{50}$-rats | 0.6 mg/l (six hours) (TOX Cat II) | MINIMUM |
| 90-day-rats (by gavage) | NOEL ≥10 mg/kg/day (HDT). Some minor body weight decreases, significance is questionable | MINIMUM |
| 90-day-dog (gelatine capsule) | NOEL = 1.0 mg/kg/day<br>LEL = 2.5 mg/kg/day<br>signs of nervous system stimulation, gastrointestinal disturbance. | MINIMUM |
| Teratology-mouse | Not teratogenic at up to and including 10.0 mg/kg/day (HDT). Possible delayed ossificaton in all treated groups. | MINIMUM |

| Study | Results | CORE Classification |
|---|---|---|
| Teratology rat | Not teratogenic at up to and including 10.0 mg/kg/day (HDT). Delayed skeletal ossification at this level. | MINIMUM |
| Teratology-rabbit | Not teratogenic at up to and including 16 mg/kg/day (HDT). Embroyo toxicity indicated at this level. | MINIMUM |
| 3-Generation Reproduction-rats | No effects at 50 ppm (HDT). | MINIMUM |
| Chronic feeding/ Oncogenesis-rats | NOEL = 20 ppm, LEL = 50 ppm decrease in body weight gain. Not oncogenic at up to and including 50 ppm (HDT). | MINIMUM |
| 2 yr. Chronic Feeding-Dog | NOEL $\geq$40 ppm (HDT). | MINIMUM |
| Oncogenesis - mice | No effects at 100 ppm (HDT). Toxic and oncogenic potential of this chemical not assessed by this study. | SUPPLEMENTARY |
| Neurotoxicity-hens | Not neurotoxic at doses up to and including 5000 mg/kg. | GUIDELINES |
| Inhalation - 21 day (14 x 6 hours) - rats | NOEL = 3.0 ug/l, LEL = 9.6 ug/l signs of irritation, and stimulation of the nervous system, effects on weight gain and elevation of serum $Na^+$. | GUIDELINES |
| Mutagenesis- E. Coli (Slater and Bridges strains) | Not mutagenic up to 5000 ug/ml. | N/A |

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| Study | Results | CORE Classification |
|---|---|---|
| Mutagenesis - Ames test | Not mutagenic with or without metabolic activation to strains TA98, TA100, TA1535, TA1537, TA1538. | N/A |
| Mutagenicity - Ames test (second study) | Not mutagenic with metabolic activation to strains TA98, TA100, TA1535, TA1537 and TA1538. | N/A |
| Mutagenesis- Dominant Lethal-mouse | Not mutagenic | N/A |
| Mutagenesis - Chinese hamster ovary cells for chromosomal aberrations. | [Studies did not give a positive response but were considered unacceptable by Toxicology Branch] | N/A |
| Mutagenesis - mouse micronucleus test. | [Studies did not give a positive response but were considered unacceptable by Toxicology Branch] | N/A |
| Microsomal metabolism in vitro. | Oxidative and hydrolytic enzyme metabolism reported and metabolites studied. | N/A (in vitro) |
| Metabolism in the mouse. | Metabolism and excretion studied. Decamethrin is rapidly metabolized and excreted. | MINIMUM |

Note: see addendum for list of studies with products containing deltamethrin. (p. 54)

A. Acute Toxicity (Technical Decamethrin)

All studies in EPA Acc. No. 070734.

1. RU 22974-Acute Toxicity Study (Mouse-rat) by the Oral Route. Roussel UCLAF Research Centre, March 30, 1976, # TOX 76810/A TAB C-1.

2. RU 22974-Acute Toxicity Study by Oral Route in Male and Female Beagle Dogs. Roussel UCLAF Research Centre, March 17, 1977 # 77804/JL-5. TAB C-3.

3. RU 22974-Acute Toxicity Study (Mouse-Rat) by Intraperitoneal Route. Roussel-UCLAF, March 30, 1976, TOX 76811/A. TAB C-4.

4. RU 22974-Acute Toxicity Study (Mouse-Rat) by Intravenous Route. Roussel UCLAF March 30, 1976 # TOX 76812/A TAB C-5.

## ACUTE ORAL TOXICITY - TECHNICAL DELTAMETHRIN

Study No. 1

| Species | Sex | N/group | Solvent | Results |
|---|---|---|---|---|
| Mice | male | 10 | Polyethlene glycol | 20.6 mg/kg (17.3-24.8) |
| Mice | female | 10 | " " | 18.7 mg/kg (15.7-22.4) |
| Mice | male | 10 | Sesame Oil | 33.1 mg/kg (27.2-40.8) |
| Mice | female | 10 | " " | 34.4 mg/kg (28.4-42.0) |
| Rat | male | 10 | Polyethlene glycol | 66.7 mg/kg (53.0-83.9) |
| Rat | female | 10 | " " | 86.0 mg/kg (70.6-106.2) |
| Rat | male | 10 | Sesame Oil | 128.5 mg/kg (104.9-156.5) |
| Rat | female | 10 | " " | 138.7 mg/kg (114.2-168.2) |

Study No. 2

| | | | | |
|---|---|---|---|---|
| Beagle dog | males | 3 | Polyethlene glycol | >300 mg/kg |
| Beagle dog | female | 3 | " " | >300 mg/kg |
| Beagle dog | male | 3 | Crystalline | >300 mg/kg |
| Beagle | female | 3 | " | >300 mg/kg |

Signs of intoxication included hypermotility, stereotyped movements of the head, tachycardia, convulsions, motor uncoordination (in rats), and stiffness of the hind legs (dogs). Mice recovered in 48 hours, rats recovered in 3 days and dogs recovered in 24 hours. These studies are CORE SUPPLEMENTARY. No necropsy was performed.

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Study No. 3

Acute Toxicity - by the Intraperitoneal and intravenous routes to rats and mice

| Species | Sex | | |
|---|---|---|---|
| Intraperitoneal | routes | Solvent | Results |
| Mice | Male | PEG-200 | 18.0(14.5-22.9) mg/kg |
| Mice | Female | " | 12.0(10.0-14.2) mg/kg |
| Mice | Male | Sesame Oil | 171.2 (153.0-191.5) mg/kg |
| Mice | Female | " | 165.6 (143.6-188.5) mg/kg |
| Rat | Male | PEG-200 | 23.7(18.6-30.1) mg/kg |
| Rat | Female | " | 25.3(18.1-35.3) mg/kg |
| Rat | Male | Sesame Oil | 208.8 (174.8-240.6) mg/kg |
| Rat | Female | " | 185.5 (151.4-212.3) mg/kg |

Study #4

Intravenous-route

| | | | |
|---|---|---|---|
| Mice | Male | PEG-200 | 4.1 (3.9-4.2) mg/kg |
| Mice | Female | " | 4.0 (3.8-4.2) mg/kg |
| Rats | Male | PEG-200 | 3.3 (2.9-3.7) mg/kg |
| Rats | Females | " | 3.3 (2.9-3.8) mg/kg |

Toxicity symptoms in mice included jumping movements, alternating periods of slight convulsions and prostration, palpebral ptosis, tail hypertonicity and cyanosis. The mice were reported as normal 22 hours after injection. In rats, the toxic symptoms included alternating convulsive tremors prostration and cyanosis and stereotyped behavior. The rats were reported as being normal 48 hours after dosing.

Following intravenous injections the mice showed tremors and convulsions and other signs. Symptoms subsided 4 to 5 hours later. In rats, deaths occurred within 10 min. Symptoms included muscular contraction, respiratory defects etc.

SUPPLEMENTARY DATA - No necropsy.

Acute Percutaneous Toxicity to Rats of Decamethrin

Huntingdon Research Centre, # RSL-10098/D147/79/A, February 21, 1979 EPA Acces. No. 070734, TAB C-6.

A single dose group of 10 rats (5 males and 5 females) were dosed with 2.94 gm/kg Decamethrin in aqueous methyl-cellulose after being prepared by clipping. The test material was kept in place for 24 hours.

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No deaths resulted nor were there behavioral signs of toxicity noted. Body weight gain was depressed during the first week in the female groups. Terminal autopsy was reported as being within normal limits.

This study is CORE MININUM. An $LD_{50}$ of >2.94 gm/kg is established. Note data are in summary form only.

RU 22974-DECIS Highly concentrated technical product (98% active material) Acute Toxicity in the rabbit by percutaneous administration.

IFREB, Jan. 2, 1977 # 770257.1/A, EPA Acc. No. 070734 TAB C-7.

A single group of 20 (10 male and 10 female) New Zealand White rabbits were prepared by clipping and were dosed with 2.0 mg/kg of RU 22974 (98% decamethrin) and kept in place for 24 hours.

No mortalities resulted. No behavioral abnormalities were observed. Some transient erythema developed. Only slight changes in bodyweight were noted. No treatment related changes were noted in the liver or kidneys.

This study is CORE MINIMUM. An $LD_{50}$ of >2.0 gm/kg is noted.

RU 22974-Test to determine primary cutaneous irritiation in the rabbit.

IFREB, # 761157/A, Nov. 15, 1976.
EPA Acc. No. 070734, TAB C-11

In these experiments, 12 rabbits (males) were prepared by prior clipping and abrading and then dosed with 0.5 ml of test product (or 0.5 gm). The test material was kept in place for 23 hours and the response then evaluated at 24 hr, 48 hr, and 72 hr later. The following table shows the results.

| Sample | Primary Cutaneous Irritations Score | TOX Cat. |
|---|---|---|
| Decamethrin - 98% | 0 | IV |
| DECIS EC 2.5 | 1.98 | III |
| DECIS EC 2.5 (1/1000 dil) | 0.04 | (IV) |
| DECIS EC 2.5 (solvent only) | 1.33 | (III) |
| DECIS ULV | 0.13 | IV |
| DECIS ULV (solvent only) | 0.27 | (IV) |

These data are CORE MINIMUM. The technical dacamethrin and its formulations (DECIS EC 2.5 and DECIS ULV) are shown to be non-irritants. Toxicity category IV or III (DECIS EC 2.5).

RU 22974 Test to evaluate ocular irritation in the rabbit.

IFREB, # 761158/A, Nov. 15, 1976.
EPA Acc. No. 070734, TAB C-12

In these studies, 12 male rabbits were dosed with 0.1 gm or 0.1 ml of test material into one eye and were observed for reactions for 7 days afterward. Six of these rabbits were rinsed 1 min after instillation. Technical decamethrin and its formulations were tested. The following table summarizes the results.

| Test Material | Reaction | Tox Cat. |
|---|---|---|
| Decamethrin - 98%<br>Decamethrin - 98% - rinsed | No corneal involvement<br>Initial reversible - irritation | III |
| DECIS E.C-2.5<br>DECIS E.C-2.5 rinsed | Corneal opacity not reversed in 21 days (less effect when rinsed) | I |
| DECIS E.C-2.5 (1/1000) | (minimal irritation) | N/A |
| DECIS E.C-2.5(solvent) | Corneal opacity not reversed in 21 days (less effect when rinsed) | N/A |
| DECIS ULV | No corneal involvement | III |
| DECIS ULV (rinsed) | Initial reversible irritation | |
| DECIS ULV (solvent) | Slight corneal involvement (one rabbit), Initial reversible irritation | N/A |

These studies are CORE GUIDELINES. The technical decamethrin is TOX Cat. III, DECIS 2.5 E.C. is Tox Cat I and DECIS ULV is Tox. Cat. III.

RU 22974-Acute Inhalation Toxicity in rats, 6 hour $LC_{50}$.

Huntingdon Research Centre, RSL 310/78453/A, May 15, 1978
EPA Acc. No. 070734 TAB C-9.

Five groups of 7 male and 7 female albino rats (Charles River CD) were exposed to dusts of decamethrin (lot 6E-0861, purity not stated) at concentrations (as determined gravimetrically) of 0 (air only), 0.049, 0.43, 0.54, and 0.72 $gm/m^3$ for six hours. The dust was produced by a Wright dust generator and the exposure chamber was 130 liters. The nominal concentrations determined by weight of material displaced and the volume of air used were 0, 0.39, 1.31, 2.07 and 2.03 $gm/m^3$. Gravimetric estimation was made by sampling the atmosphere (6-8 times) and collecting the dust on preweighted paper. The particle size of the dust generated was determined using an Andersen Mini-Sampler. This system showed that the atmosphere consisted of 69-88% particles of respireable size (<5.5 um).

An $LC_{50}$ (6 hours) was determined to be 0.6 $gm/m^3$ (using the atmospheric concentration obtained by gravimetric analysis).

The signs of toxicity included irritation (both nervous system signs and dust response), hyperactivity, pytalism (excessive salivation) and modified diaphramatic breathing. Hypersensitivity and ataxia were noted especially preceding deaths. Some of these signs persisted up to 10 days.

Necropsy revealed elevated lungs/bodyweight ratio in the dead rats and signs of hemorrhage which increased with the dose level.

The lowest dose level tested (0.049 $gm/m^3$) showed "moderate" signs of ptyalism and other signs of irritation. This level was chosen to try to demonstrate a NOEL.

This study is CORE MINIMUM. The technical material is TOX Cat. II.

RU 22974- I. Respiratory tolerance (Decis 2.5EC) in the guinea pig in closed chamber system. II. Respiratory tolerance in the guinea pig in open circuit system. III. $LC_{50}$ in rat and mouse by inhalation in open circuit system (Decis 2.5EC).

IFREB, # 761154/A, Nov. 15, 1976
EPA Acc. No. 070734, TAB C-10

Part I

Eight guinea pigs (4 males and 4 females) were exposed to vapors of decamethrin (as DECIS 2.5 formulation - concentrate) in an unventilated chamber for 4 hours. The amount of test chemical in the exposure was 7.42 gm (over a 4 hour period). The guinea pigs reportedly tolerated the exposure well except for noticable ocular and nasal mucous irritation. Autopsy of the treated guinea pigs was unremarkable.

Part II

Eight guinea pigs (4 male and 4 females) were exposed to vapors from decamethrin (as DECIS EC 2.5 or DECIS ULV) for 4 hours. The mean concentration of DECIS 2.5 EC was 15 $ml/m^3$ (for 4 hours) and this condition resulted in no behavioral changes or mortalities. Exposure to 22.5 $ml/m^3$ of DECIS ULV resulted in rapid onset of a variety of symptoms including dyspnea. All pigs died. Exposure to 1.9 $ml/m^3$ of DECIS ULV resulted in signs of sneezing (respiratory irritation) but no deaths developed. No abnormalities at necropsy were noted in guinea pigs which survived exposure.

III. ($LC_{50}$ determination of DECIS 2.5 E.C.)

Ten rats or mice (5 males and 5 females) were exposed to vapors of DECIS 2.5 EC for 3 or 4 hours at a concentration of 5.5 $ml/m^3$.

No mortalities of either rats or mice occurred.

The symptoms were more pronounced in mice and included intense activity, hyperexcitability to noise, chronic spasms followed by atony.

The $LC_{50}$ for this formulation was determined to be >5.5 $ml/m^3$. Autopsy did not reveal unusual lesions.

The data from the studies with guinea pigs are CORE SUPPLEMENTARY. The $LD_{50}$ study with rats with the test substance Decis 2.5EC is CORE MINIMUM data and this product is Toxicity Category III.

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RU 22974-Assessment of Toxicity to rats by oral administration for 13 weeks (by gavage) (followed by a 4 week withdrawal period.)

Huntingdon Research Centre, RSL254/76938/A3, Mar. 21, 1977
EPA Acc. No. 070736, TAB C-29

Five groups of CD strain (Sprague-Dawley origin) rats each with 20 males and 20 females were dosed daily by gavage with 0, 0.1, 1.0. 2.5, or 10.0 mg/kg of RU 22974, (lot and purity were not stated) in polyethylene glycol 200 for 13 weeks. After 13 weeks, the rats (except for 5 males and 5 females per group) were sacrificed and examined. The remaining rats were allowed 4 weeks to recover from any effects of dosing.

Results

1. Mortality - no dose related increase in deaths were noted. Several rats died during the first few weeks. Rats which died during the first two weeks only were replaced. The cause of death was reported as resulting from injecting the test material into the lungs. Because of the occasional deaths, the original dosing volume of 5.0 ml/kg was reduced to 2.5 ml/kg.

2. Body weight change and food and water consumption. Body weight differences are shown in the following table.

BODY WEIGHT

| Week/Dose Level | Males | | | | | Females | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 0.1 | 1.0 | 2.5 | 10.0 | 0 | 0.1 | 1.0 | 2.5 | 10.0 |
| 0 | 152 | 152 | 153 | 152 | 152 | 132 | 132 | 132 | 132 | 132 |
| 6 | 417 | 420 | 414 | 405 | 395 | 262 | 257 | 263 | 269 | 265 |
| 13 | 540 | 538 | 517 | 509 | 504 | 303 | 299 | 302 | 310 | 302 |
| Recovery 17 | 557 | 611 | 587 | 562 | 574 | 307 | 310 | 338 | 342 | 328 |

The above table shows that there is no difference in the bodyweights of the females. The male groups are lower except for the group dosed at 0.1 mg/kg. The weights of the group receiving 1.0 mg/kg are lower at week 13, but the difference is not statistically significant (t test as presented in the report). The depressions noted at 2.5 mg/kg (-6%) and 10.0 mg/kg (-7%) were noted to be statistically significant. The net weight gain for 0-13 weeks was also statistically significantly lower for the mid- and high-dose test groups.

The rats which were allowed to recover gained weight at a rate better than or equal to the control groups.

There were no consistent effects noted related to food consumption, efficiency of food utilization or water intake.

3. Clinical signs and neurological analysis (including ophthalmoscopy) Neurological examination was evaluated for the rats in the control groups and in the groups receiving 10 mg/kg before treatment, at weeks 7 and 13. Ten males and 10 females from each group were examined. The assessment consisted of segmental reflex - (flexor, extensor, patellar); postural reactions (righting reactions: optic and general), placing reactions, extension thrust and grip reflex; and locomotor systems (gait and muscles). The report states that no overt signs of reaction to treatment were recorded. There was, however, some evidence that the rats receiving 10.0 mg/kg were slightly hypersensitive. There was no evidence of treatment-related ocular damage as observed by examination with a Keeler indirect ophthalmoscope.

4. Urinalysis (5 males and 5 females from the controls and high dose group) were evaluated at weeks 6 and 12. Analysis included pH, specific gravity, protein, reducing substances, glucose, ketones, bile pigments, urobilinogen and hemoglobin and microscopy of the spun deposit. No abnormalities related to administration of the test chemical were noted.

5. Hematology - during weeks 6 and 12, samples of blood were drawn from the orbital sinus of 10 males and 10 females from the controls and the high dose group. Analysis included: PCV, Hb, RBC counts, mean corpuscular haemoglobin concentration and mean cell volume, total white cell and differential cell count, platelet count and thrombotest were made at week 12 only. No consistent dose related effects of the test chemical were noted.

6. Blood chemistry - during weeks 6 and 12, samples of blood were withdrawn from the orbital sinus of 5 males and 5 females from the controls and the high dose test groups. Analysis included: plasma urea, glucose, total serum proteins and electrophoresis, SAP, SGPT, $Na^+$ and $K^+$. No consistent dose related effects of the test chemical were noted.

7. Organ weights - absolute and relative organ weights were determined for the adrenals, brain, heart, kidneys, liver, ovaries, pituitary, spleen, testes, thyroid and uterus. No consistent dose-related effects of the test chemical were noted.

8. Gross necropsy. These data are presented in an abbreviated form. Only animals with lesions are indicated

with a description of this lesion. Only four rats of the 100 males and 2 rats of the 100 females are reported as having grossly observable lesions. The two females were in the high dose group and both had the uterus "minimally enlarged" and the ovaries "congested."

9. Histology - Microscopic examination of the controls (9 males and 9 females) and the high dose group (10 males and 10 females) and selected other animals showing gross lesions, was conducted. 37 tissue types were preserved in fixative. No complete report of the microscopic findings was included. Only for tissues found to have some evidence of a microscopic lesion were there descriptions, except that the results of the liver, nervous system and musculature were usually described.

   No treatment-related lesions were noted. The slides of nervous system and musculature for the controls and high dose groups were sent to Dr. J. B. Cavanagh, a noted authority on neuropathology, for evaluation. Dr. Cavanagh expressed the opinion that the treated rats did not show evidence to suspect that there was peripheral nerve pathology present.

CONCLUSION:

This study is CORE MINIMUM. The dose levels selected did not produce data sufficient to assess the toxicological effects of this chemical, other than for depression of body weight gain. A NOEL is set at 1.0 mg/kg/day. The LEL (for depression of body weight) is 2.5 mg/kg/day.

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RU 22974- Oral toxicity (Gelatin Capsule) study in Beagle dogs (Repeated dosage for 13 weeks followed by a 20-week recovery period).

Huntingdon Research Centre, # RSL 253/77251/A3, June 8, 1977. EPA Acc. No. 070736, TAB C-30 and C-31

Five groups of beagle dogs (pure bred) were dosed with RU22974 (decamethrin, a white powder from lot #17, the purity was not specifically stated), at dose levels of 0, 0.1, 1.0, 2.5 and 10.0 mg/kg/day. Dosing was by gelatine capsule of the test material in polyethylene glycol (0.2 ml). The control and low dose groups consisted of 3 males and 3 females. The other groups ocnsisted of 5 males and 5 females. Dosing was for 13 weeks. After 13 weeks the dogs were sacrificed except for 2 males and 2 females in the three highest dose groups. The dogs which were not sacrificed were allowed to continue an additional 20 weeks for recovery of any toxic effects.

Results:

1. There were no deaths. Signs of reaction to the test chemical included (i) unsteadiness, body tremors and jerking movements, (ii) vomiting, (iii) excessive salivation, (iv) passing of liquid feces, and (v) dilation of the pupils. The three sets of symptoms above, related primarily to the effects of the test chemical on nerve tissue, occurred in the high dose group (with the possible exception of dilation of the pupils occurring in the 2.5 mg/kg dose gorup). These signs did not occur in the dogs during the 20 week recovery period.

   The symptoms primarily related to the gastrointestinal tract (vomiting and the passing of liquid feces) have a dose related effect as shown.

| | Total incidences of vomiting | | Total incidences of passing of liquid feces |
|---|---|---|---|
| | dogs* | | |
| Control | 6 | 2 | 35 |
| 0.1 mg/kg | 6 | 3 | 42 |
| 1.0 mg/kg | 10 | 8 | 82 |
| 2.5 mg/kg | 10 | 11 | 197 |
| 10.0 mg/kg | 10 | 47 | 292 |

* Combined male and female data for weeks 1-13 only.

These data indicate a NOEL of 1.0 mg/kg/day. At 2.5 mg/kg/day (LEL) signs of gastro-intestinal disturbance are noted. At 10.0 mg/kg/day definite signs of nerve stimulation (behavioral) are noted.

2. Body weight gain and food and water consumption. A NOEL is set at 2.5 mg/kg/day by the testing laboratory for decreased body weight and decreased food consumption. Note: This reviewer considers that the number of dogs per dose level precludes making valid conclusions related to these parameters.

3. Ophthalmoscopy (determined on five occasions) predosing, weeks 6 and 13 during test and on weeks 6 and 19 during recovery. No effects of the test substance noted.

4. Neurological examination (EEG, pupillary light reflex, blink reflex, corneal reflex, gag reflex, flexor reflex, crossed extensor reflex, extensor reflex, patellar reflex, tonic neck reflex, extensor postural thrust, righting reactions, placing reactions, and hopping reaction were evaluated). Examinations were made at predosing, at 5 and 12 weeks of dosing and during recovery. (Note: This reviewer considers that the number of dogs per sex per dose level especially concerning the recovery phase of this study seriously limits the usefulness of the data.)

   The report presents evidence that some effects of the test chemical (depression of the flexor reflex and exaggeration of or depression of the patellar reflex) particularly in the dogs receiving 2.5 and 10.0 mg/kg/day. Similarly EEG analysis also revealed effects at these dose levels. Analysis of the dogs which were allowed to recover revealed that a single dog receiving the high dose level showed some evidence of possible sustained neurological damage.

5. Laboratory Investigations: (all available dogs were tested at predosing, after 6 and 12 weeks on test and after allowing 5 and 16 weeks for recovery).

   Haematology included: erythrocyte sedimentation rate, PCV, Hb, RBC count, reticulocyte count, MCHC, MCV, total white cell count, differential white cell count, platelet count and prothrombin index.

   Biochemistry included: plasma urea, glucose, total serum proteins (electrophoresis and AG ratio), SAP, SGPT, SGOT, bilirubin and $Na^+$ and $K^+$ determinations.

Urinalysis included: specific gravity, pH, protein, reducing substances, ketones, bile pigments, urobilinogen and hemoglobin and microscopy.

No consistent dose related findings were noted or reported with regard to the above hematological, biochemical or urinalysis parameters.

6. Organ Weights (brain + spinal cord, pituitary, heart, lungs, liver, spleen, pancreas, thymus, prostrate/uterus, kidneys, thyroids, adrenals, and gonads).

   No effects on the weights of these organs were noted or reported. Note: Since only 3 dogs of each sex were used for each dose group only a large difference would have been noted.

7. Gross necropsy: No lesions were reported as being related to ingestion of the test substance.

8. Histology - 36 different organ samples from each dog were reported as being analyzed histologically. No dose related effects were noted. The lesions that were reported were those which commonly occur in the beagle dog. The nerve tissue was especially examined by Dr. J. B. Cavanagh, a noted authority on chemical induced neuropathology. His analysis was that the findings in nerve tissue were not related to dosing with the test chemical.

   This study is CORE MINIMUM. A NOEL of 1.0 mg/kg/day is supported. At higher levels stimulation of the nervous system is noted (the LEL is set at 2.5 mg/kg/day but effects were more definitely at 10 mg/kg).

   The recovery phase aspect of this study is somewhat limited in its usefulness because no control dogs were included.

RU 22974-Toxicological study in the pregnant female (mouse, rat, rabbit)(teratology)

Roussel UCLAF Research Centre, # 75583, 75584, 75585-JL19/A - January 5th, 1976 and 76534, 76536/2/A EPA Acc. No. 070735. TABS C-17, C-18, C-19

Preliminary experiment-

A preliminary experiment indicated that dose levels of 0.1, 1.0 and 10 mg/kg/day are appropriate levels for teratology studies in the mouse and rat. Levels of 1, 4 and 16 mg/kg/day are appropriate for the rabbit.

Dose levels of 14 mg/kg/day in mice and 21 mg/kg/day in the rat gave signs of toxicity, including deaths. The rats were paralyzed in their hindquarters. There were no signs of toxicity reported in rabbits dosed with 50 mg/kg/day. Fetal loss was evident at 14 mg/kg day in mice and also in the rats dosed with 21 mg/kg/day.

Part 1 - Mouse

Four groups of 24 female CD 1 Specific Pathogen Free mice were dosed with 0, 0.1, 1.0 on 10 mg/kg/day during days 6 to 17 of gestation. The mice were previously mated by placing the females in the presence of males. The mice were sacrificed on day 18 by $CHCl_3$ inhalation. Half of the fetuses were fixed in Bouin's fluid for external examination, the remainder were fixed in alcohol and stained for skeletal examination.

1. Effects on the dams. Although four females died (3 mid- and a high-dose group female) there were no signs of toxicity due to the treatment. Body weight gain and conception rate were reported as being equivalent for controls and treated females. The conception rates were 87.50, 87.50, 75.0, and 79.16 for the control, low, mid and high dose groups.

2. Litter data:

   There were 199, 217, 193 and 190 total living fetuses for the control, low, mid and high dose test groups. There were no dose-related differences in total implantations or fetal losses. The average fetal weights were 1.35, 1.28, 1.26* and 1.24* (*these values were statistically significant at the $p<0.05$ level, Dunnett's test).

3. Examination of the fetuses (data presented in summary form only).

   i. These were 2 incidences of exencephalica (a control and a low dose group) noted on external examination.

   ii. There was a single incidence of cleft palate (mid dose group) noted on internal examination.

   iii. There were occasions of delayed ossification noted in the skeletal, sternebrae and paws. These reached statistical significance in all dosed groups, but the laboratory maintained that the frequency was within normal variation for this strain of mouse.

   This study is CORE MINIMUM. The NOEL for teratogenic effects in mice is $\geq$10 mg/kg (HDT). The increased incidences of delayed ossification together with the depression in fetal weight may indicate a fetotoxic effect. No positive control was run concurrently and there were no signs of pronounced toxicity in the dams.

Part 2 - Rat

Four groups of 24 female Sprague-Dawley rats were dosed with 0, 0.1, 1.0, or 10.0 mg/kg/day of decamethrin (batch #18, in sesame oil) on days 6-18 of gestation. The rats were previously mated with proven males of this strain. On day 21 of gestation the rats were sacrificed by $CHCl_3$ inhalation. Half of the fetuses were saved for soft tissue examination (fixed in Bouin's solution) the remainder were fixed in alcohol and later examined for skeletal defects.

Results:

1. Effects on dams. There were no deaths or signs of toxicity reported. Bodyweight in the 10 mg/kg dose groups was reduced slightly (approx. 10%, the actual individual rat bodyweights were not presented in this report).

2. Litter data:

   The conception rates (or pregnancy rates) were 66.7, 87.5. 87.5, and 83.33 for the controls, low, mid and high dose test groups. Total fetal losses were 5, 7, 8 and 10 and there were 223, 262, 287 and 242 live fetuses per group for the controls, low, mid and high dose test groups. Expressed as a percentage there was an average fetal loss of 2.19, 2.60, 2.71 and 3.97 for the control, low, mid

and high dose test groups. The average fetal weight was near 5.31 gm for all groups.

3. i. External examination revealed only a single incidence of polydactyl (in a control pup).

ii. There were no internal abnormalities reported.

iii. Skeletal examination revealed a statistically significant increase in delayed ossification of the sternebrae in the high dose test group.

Lactation and other aspects of maternal performance were also assessed in the rat. Twelve control and 12 rats dosed with 10 mg/kg/day were delivered and the pups allowed to grow. There were no significant differences noted in gestation period, total number of living pups at birth, at day 4, or at day 21. The viability index was 92.0% for the controls and 90.4% for the high dose test group. The lactation index was 90.7% for the control and 90.4% for the treated group. The rats treated with decamethrin showed a slightly lower body weight as follows at day 7: -4%, at 14:-3%, at day 21:-6%; at day 28:-4%. These weight differences are not definitely related to the treatment with the test chemical.

This study is CORE MINIMUM. Decamethrin was demonstrated not to show teratogenic effects at doses up to and including 10 mg/kg/day (HDT) in the rat. A possibly fetotoxic effect was noted at 10 mg/kg/day (delayed ossification of the sternebrae). No positive control was included. The data are in summary tables only.

Part 3 - Rabbit

Five groups of female New Zealand White Strain rabbits were mated and dosed with either 0, 1, 4, or 16 mg/kg/day of decamethrin (lot #18 in sesame oil). There were two separate groups which received the dosing of 16 mg/kg/day. There were originally 15 rabbits per group and they were dosed on days 6-19 of gestation. The rabbits were sacrificed on day 28 of gestation and the uterine contents examined. The fetuses were divided approximately so that one half was prepared and examined for soft tissue abnormalities and the other half was examined for skeletal abnormalities.

Results:

1. Two of the rabbits dosed with 16 mg/kg/day died. These rabbits showed evidence of having pneumonia. Thus, there was no evidence presented that treatment affected the rabbits to produce toxic signs. Body weight gain was considered to be equivalent in all groups (gains were 10% to 14% between days 0 and 28).

2. Litter data:

   There were 11-15 pregnant rabbits per dose group. Females found with no living conceptus were noted only in the dosed animals and not in the control.

   There was evidence presented to suggest that decamethrin treatment resulted in fetal losses. For example, when expressed as average fetal losses (%) per group the following pattern is noted: 6.6, 18.5, 15.5, 10.2, 27.4, for the control, low, mid and two high dose test groups. Other evidence for an effect is an apparent decrease in pup body weight: -8%, -4%, -14% and -13% relative to the control for the low, mid and two high dose test groups respectively.

   There were no patterns to indicate that decamethrin produced teratogenic effects in the pups examined. There were 99, 66, 71, 97 and 69 total pups available for examination for the control, low, mid and two high dose test groups.

   This study is CORE MINIMUM. [No positive control was included. The data are in summary form only.]. Deltamethrin is shown not to be teratogenic at doses up to and including 16 mg/kg/day. Embroyo toxicity (fetal losses and decreased pup body weight) are noted at 16 mg/kg/day (HDT).

003066

Three generation reproduction study in rats

IRDC, # 406,003/A4, Feb. 5, 1980
EPA Acc. No. 070735, TAB C-20

Four groups of 10 male and 20 female Charles River CD rats were initiated as the $F_0$ parental generation and dosed with 0, 2, 20 and 50 ppm of decamethrin (RU-22974 lot 22) in their diets. From these rats successive $F_{1a}$, $F_{1b}$, $F_{1c}$, $F_{2a}$, $F_{2b}$, $F_{3a}$ and $F_{3b}$ generations were produced. Because of technical difficulties, it was necessay to produce a $F_{1c}$ generation. The special aspects for a reproduction study which were evaluated were male and female fertility, length of gestation period, number of male and female pups at weaning and the viability, growth and survival of the pups through weaning. Also the number of pups surviving at lactation days 0, 4, 14 and 21 was determined. After weaning, all surviving $F_0$, $F_1$, and $F_2$ generation parents and 5 male and 5 female $F_{3b}$ generation weanings were necropsied and organ weights determined and histopathology was performed.

Results:

1. Effects on the parental generations: No adverse effects were noted. All groups produced litters at similar frequencies: there were no differences in length of gestation or other signs of effects on the males or females to indicate an adverse effect on reproductive performance noted. The $F_0$ generation high dose group showed 10% lower bodyweight gain starting at weeks 11 to 39. This effect was not noted for the $F_1$ and $F_2$ parental generations and is not considered to be definitely related to the test chemical.

2. Litter data:

   There were noted some occasions of decreased litter weights at lactation day 21 but neither the consistancy over the three generations nor the magnitude of the decrease nor its relationship to the dose level of the chemical in the diet allow the conclusion that these decreases were related to the test chemical.

3. Organ weights (for the necropsied $F_{3b}$ generation weanlings): the weights of the adrenals, kidneys, thyroids/parathyroids, hearts, livers, spleens and testes or ovaries were weighed. No consistent changes in the weights of these organs were noted which indicated a dose response relationship.

4. Pathology:

There were no indications of either gross necropsy or histopathological lesions noted for those rats examined ( 45 tissues from each rat were reported as being examined histologically).

This study is CORE MINIMUM. A NOEL of 50 ppm is assigned. The highest dose level tested did not produce significant pharmacological or toxicological responses thus precluding assignment to a higher CORE classification.

003066

TWO YEAR ORAL TOXICITY AND CARCINOGENICITY STUDY IN RATS

IRDC, # 406-002/A4, May 6, 1980
EPA Acc. No. 070737 and 070738, TAB C-32

Decamethrin (Lot 22, precise purity not stated) was incorporated into the diets of Charles River CD rats at the concentrations of 0, 2, 20 and 50 ppm. There were 4 groups of 90 males and 90 females and a fifth group of 60 males and 60 females. The first four groups were dosed as control, low dose, mid dose and high dose decamethrin treated rats. The fifth group was a control group. Ten rats of each sex from each group (except the fifth group as above) were sacrificed at 6, 12 and 18 months and evaluated at these times for toxic effects.

Results:

1. Survival - 50% to 63% of the males and 50-67% of the females survived the 2 year dosing period. Thus, there were always 30 or more rats available for terminal evaluation for all dose groups. There was no trend or other indication that decamethin treatment affected the survival.

2. General behavior - no signs of intoxication were reported. Treated animals were reported as being in the same physical condition as the controls.

3. Body weight - there was a minor depression of body weight gain noted in both sexes as shown in the following table.

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| | Combined Control | Low | Mid | High | Combined Control | Low | Mid | High |
| Week | | | | | | | | |
| 26 | 621 | 621 | 607 | 596* | 324 | 321 | 329 | 314 |
| 52 | 737 | 727 | 720 | 699* | 383 | 390 | 395 | 366 |
| 78 | 783 | 775 | 767 | 738* | 464 | 460 | 476 | 432* |
| 104 | 777 | 765 | 771 | 724* | 502 | 517 | 501 | 463 |

*Shown by the report to be statistically significantly different from one or the other of the control groups. Data are in grams.

The high dose group males and females are 3-7% lower than the controls.

There was no corresponding decrease in food consumption. A NOEL for depression of body weight gain is set at 20 ppm.

4. Ophthalmoscopy - appraisals were made at pretest and at 6, 12, 18 and 24 months. No consistent effects of the test chemical were reported.

5. Laboratory tests were appraised at pretest, at 6, 12 and 18 months using 10 rats/sex/dose and at 24 months using 20 rats/sex/dose.

   Hematology included hematocrit, Hb, total erythrocyte count, total and differential leucocyte counts, total platelet count, reticulocyte count, Heinz bodies and methemoglobin.

   Biochemical values included glucose, protein, electrophoresis of serum proteins, BUN, alkaline phosphatase, SGPT, $Ca^{2+}$, $Na^{+}$, $K^{+}$, $Cl^{-}$ and inorganic phosphate.

   Urinalysis included: volume, pH, specific gravity, appearance, albumin, glucose, ketones, bilirubin, urobilinogen and occult blood and microscopic evaluation of the sediment. With the exception as indicated below, there were no consistent dose related effects of the test chemical on these parameters.

   SGPT was found to be lower in the mid and high dose test groups at six months. The males were about 50% lower and the females were also about 50% lower. (The male data were barely readable in this report.) This depression was noted only at the 6th month and not at the other times. This is not considered a toxic response to the chemical. For example, SGPT values are more likely to go up as a result of tissue injury.

Pathology

1. Gross necropsy. The several gross necropsy tables presented did not indicate that there was a treatment-related increase in grossly observable lesions.

2. Organ weights (spleen, liver, kidneys, testes/ovaries, prostrate/uterus, heart, lungs, thymus, adrenals, thyroid and pituitary) were weighed at 6, 12, 18 and 24 months. No consistent dose-related increases or decreases in absolute or relative weights were noted.

3. Microscopic pathology: Tissues from groups 1, 2, 3, and 4 were prepared by IRDC personnel but tissues from group 5 (the extra control group) were prepared by American Histolabs Silver Spring, Maryland. Note: refer to Appendix I of this memo for further discussion as to where tissues were prepared. For most animals, all available tissues from the controls and high dose groups (both sexes/both groups) were prepared for microscopic observation. The low and mid dose animals had tissues prepared and examined apparently only in response to gross necropsy observations.

   The pathology report was signed by Dr. Reynaldo J. Arceo and Dr. Eric J. F. Spicer of the IRDC. The individual responsible for the diagnosis of each slide was not specifically stated.

Oncogenic Aspects

1. The following table summarizes the overall neoplastic findings.

| | Males | Females |
|---|---|---|
| Control - 1 | 67/88* | 140/89 |
| Low | 45/- | 111/- |
| Mid | 44/- | 99/- |
| High | 73/90 | 119/90 |
| Control - 2 | 62/60 | 131/61 |

* Data are incidences of neoplasms/number of rats given "complete" microscopic examination. No denominator is entered for the low and mid dose test levels because these groups were not scheduled for "complete" microscopic examination.

2. Individual organ discussions for both neoplastic and nonneoplastic lesions.

   i. In both the males and females, the pituitary gland had high numbers of adenomas and a few carcinomas. Among the males there were 30/87, 22/24, 27/29, 32/89 and 27/60 adenomas for the control group 1,

low, mid, high and control group 2 dose levels. There were 2 carcinomas (one in a control and 1 in a high dose test rat). Among the females, there were 56/87, 38/40, 34/41, 56/88 and 48/61 adenomas for the test groups as indicated above. There were 4 carcinomas, two in the controls and one each in the mid and high dose groups. These data do not indicate an oncogenic effect of deltamethrin in the pituitary.

ii. There were a total of 2 incidences of liver neoplasms, one in the male mid dose group (hemangiosarcoma) and 1 incidence of hepatocellular carcinoma. Non neoplastic pathology of the liver was unremarkable.

iii. The testes has been shown to be a neoplastic target organ for at least 1 other synthetic pyrethroid when tested at higher (>1000 ppm) dosages and when the rats were exposed in utero. For the study being reviewed here with deltamethrin, there was noted a statistically significant increase in interstitical cell adenomas in the high dose test group when compared to group 1 control group. There were 0/88 in control group 1 (0%) and 7/90 (7.8%) in the high dose test group. This difference is statistically significant ($P < .01$ using Fisher's Exact Test and TB computer). This lesion is discussed further (see Appendix I of this memo.)

iv. Among the females, the mammary gland had high incidences of fibroadenoma and adenocarcinoma. There was a decrease (statistically significant) in the net adenocarcinomas in the high dose test group when compared to either of the control groups. For example there were 11/90 (12.2%) incidences in the high dose test group and 23/89 (25.8%) or 18/61 (29.5%) in the two control groups. From 33-34 percent of the control or high dose test group rats were affected with fibroadenoma.

v. In the adrenals of the males there were 4/90 (4.4%) incidences of pheochromocytoma in the high dose group, none in the control group-1, but 3 in control group 2 or 5%.

vi. Nerve tissue: There were reported some slight increases in axonal degeneration in the mid and high dose test groups noted only in the 18th month sacrifice and not in the terminal sacrifice. It was the conclusion of the laboratory that these lesions were not compound related.

All other neoplastic types were of low incidences and in a random distribution. There were no consistent or dose related increases in nonneoplastic tissue lessions.

CONCLUSION: This study is CORE MINIMUM. A NOEL is set a 20 ppm. At 50 ppm (LEL) there is noted a rather consistent decrease in body weight gain in the males. No oncogenic effects were noted at up to and including 50 ppm (HDT).

2-Year Chronic Dog Feeding Study
IRDC, # 406-004/A1, September 16, 1980.
EPA Acc. No. 070741 TAB C-34

Four groups of 8 male and 8 female beagle dogs were dosed with diets containing 0, 1, 10, and 40 ppm of decamethrin (RU 22974, CLE 6E0861) for 24 months.

Results:

The study concludes that the NOEL for any response is > 40 ppm, the highest dose level tested. Toxicology Branch concurs that there are no observed effects which describe the toxicology of this test substance. Refer to the 90 day dog study for the parameters investigated but note that not all of the extensive neurological examinations conducted for the 90 day study were investigated for this study.

Analysis of body weight and food consumption indicate that the dogs consumed decamethrin at the levels of 0, 0.026, 0.261, 1.134 mg/kg/day for males and 0, 0.024, 0.271 and 1.061 mg/kg/day for females. The 90 day study with dogs was shown to have a NOEL of 1.0 mg/kg (by gelatine capsule). This study (90 day study) also had unresolved questions related to possible neurological damage at 10.0 mg/kg/day (see review this memo). This 2 year dog study does not provide data to resolve the question as to whether decamethrin can cause neurological effects in dogs at higher doses.

These data are CORE MINIMUM. Sufficient data to support a NOEL of > 40 ppm have been generated.

RU-22974 (DECIS) Inhalation Toxicity Study in rats 14 X 6 Hour Exposures over a period of 3 weeks.

Huntingdon Research Center, RSL/318/78638/A. Oct. 19, 1978. EPA Acc. No. 070735, TAB C-15.

Four groups of CD® rats (Charles River, UK), consisting of 8 males and 8 females per group were exposed to atmospheres containing either air or one of three concentrations of decamethrin. The test material used was from lot 22 and was a fine white crystalline powder. The exposures were for six hours per day for five days a week for a total of 14 exposures. The atmospheres of decamethrin were generated by a Wright Dust generator. This generator consists of a canister into which powder is packed and a scraper head which removes the powder at a preset rate. The atmospheric concentrations of decamethrin were determined by sampling the air and collecting the dust on filter paper. The filter paper was soaked in methanol and the concentration of decamethrin was determined spectrophotometrically. Particle sizes were determined by using a series of 4 metal impaction stages and a back up glass fiber filter.

Results:

1. The atmospheric concentrations and particle size of decametrin were determined to be:

| | By Nominal Concentration | By Spectrophotometric Analysis | Particle size < 5.5 um |
|---|---|---|---|
| Control | - | - | - |
| Low | 9.8 mg/m$^3$ | 3.0 mg/m$^3$ | 87.1% |
| Mid | 18.0 mg/m$^3$ | 9.6 mg/m$^3$ | 86.4% |
| High | 117.0 mg/m$^3$ | 56.3 mg/m$^3$ | 87.2% |

2. Reactions - Signs of nerve stimulation (washing and scratching of the face, above the level indicated in the controls) were noted in all dosed groups. One rat in the low dose group displayed ptyalism; this reaction increased with the increases of decamethrin with atmospheric concentration. The rats exposed to the highest dose level reacted by walking with a arched back. Other signs noted in the high dose group and occasionally in the mid dose group included hunched posture, peripheral vasodilation, minimal aggresive behavior and hypersensitivity to noise and scarring of the ears (presumed to be related to excessive scratching). No rats died as a result of the exposure.

3. Body weight and food and water consumption. A statistically significant dose-related reduction of growth was observed for all male test dose groups. For example, there was -5% loss for the low dose group, -6% for the mid dose group and -10% for the high dose group. The females also showed evidence of reduced weight gain. The most severe effects on bodyweight gain were noted during the period immediately following the weekend break (days 10 and 11) of the study.

   The rats dosed with decamethrin also consumed less food. Water intake was variable and the males in the high dose groups consumed less.

4. Clinical pathology (hematology, urinalysis and biochemistry): the rats were deprived of food and water overnight (day 18 -19) and during this time the urine was collected. Blood samples were collected on day 19. Urinalysis included: volume, pH, specific gravity, protein, total reducing substances, glucose, ketones, bile pigments, urobilinogen, blood pigments and microscopy of the spun deposit. Hematology included: PCV, Hb, RBC count, MCAC, MCV, total and differential WBC counts, platelet count and thrombotest. Blood chemistry included: serum urea, plasma glucose, total serum proteins, serum albumin, SAP, SGPT, $Na^+$, $K^+$, $Ca^{++}$, $P_i$, cholesterol and creatinine.

   There were no consistent dose-related differences in these parameters except as indicated as follows.

   The blood levels of $Na^+$ were elevated for both sexes as indicated in the following table.

| | m E/l | |
|---|---|---|
| | Males | Female |
| Control | 142 ± 2.1 | 141. ± 0.8 |
| Low | 143 ± 2.6 (0.7%)[1] | 142 ± 2.3 (0.7%) |
| Mid | 146 ± 1.6 (2.8%)** | 147 ± 4.3 (4.3%)** |
| High | 147 ± 1.2 (3.5%)*** | 150 ± 1.9 (6.4%)*** |

[1] Figure in ( ) is percent increase
** P <.01, t test
*** P <.001, t test
also statistically significantly different by the Williams test.

Pathology

1. Organ weight (brain, pituitary, heart, liver, spleen, prostate, kidneys, thyroids, adrenals, gonads, uterus): There were no consistent differences in either absolute or relative organ weights.

2. Gross Pathology - The only compound-related grossly observable lesions were associated with scarred ears. These were allegedly due to the irritation caused by the dust in the air. Other grossly observable lesions were considered normal variations.

3. Microscopic pathology - Performed in all control and high dose group rats and involved 36 tissue types. The remaining tissues from the rats not examined were stored for possible future evaluation. The microscopic pathology evaluation was made by Lee Newman Research Associates, Highbury House, Rumsam Rd., Barnstable.

No increased incidences of a particular lesion type were noted in the high dose test group which was not also reported in the control groups.

Conclusion: This study in CORE GUIDELINES. The NOEL is set at 3.0 $mg/m^3$ or 3.0 ug/l. At higher levels there was evident signs of irritation (nerve stimulation) that were considered to be due to the test substance. Male rats also showed reduced weight gain in all groups including the low dose groups (-5%). The irritation and weight lose at 3.0 ug/l is not considered to be of sufficient magnitude to assign 3.0 ug/l as an effect level. There was also noted an elevation of serum $Na^+$ content (LEL = 9.6 $mg/m^3$).

TWO YEAR ORAL TOXICITY AND CARCINOGENICITY STUDY IN MICE

IRDC, #406-001 A/4, May 6, 1980
EPA Acc. No. 070739 and 070740, TAB C-33.

Five groups of 80 male and 80 female Charles River CD®-1 mice were dosed with 0, 1, 5, 25 or 100 ppm of decamethrin (RU 22974 lot 22, a white powder, the exact purity was not stated); a sixth group of 60 males and 60 females were also included as a control group. Interim sacrifices of the mice in the first five groups were made at 12 and 18 months when 10 males and 10 females from each group were sacrificed. The remaining mice were kept on their diets containing decamethrin for 24 months. Clinical laboratory (blood analysis and urinalysis) were conducted on 10 males and 10 females from each group at 12 and 18 months.

Results:

1. Survival: There was no evidence of a dose-related effect on the ability to survive the 2-year dosing period. There were 24 or more mice (out of 60) which survived the 24 months from each group.

2. There were no changes in the physical appearance or behavioral reactions reported for the mice which could be related to ingestion of decamethrin.

3. Body weight: Only small depressions in body weight in the high dose group (males and females) were noted. For example, at termination high dose group males were 6% lower and high dose group females were 4% lower than the combined control groups. The testing laboratory did not consider this depression to be biologically significant.

4. There were no differences in the amount of food consumed (mg/mouse/day) related to the presence of decamethrin in the diet. The males consumed 0.12, 0.61, 3.1 and 12 mg/kg/day and the females consumed 0.15, 0.76, 3.8 and 15 mg/kg/day of decamethrin for the low, mid-1, mid-2, and high dose test groups.

5. Hematology: The following values were investigated: hematocrit, Hb, total erythrocyte count, total and differential leucocyte count, total platelets, reticulocyte count, Heinz bodies, and methemoglobin.

   No consistent dose-related effects of decamethrin were noted on these parameters.

6. Biochemistry of blood: The following values were investigated: fasting blood glucose, total protein, electrophoresis of plasma protein, BUN, plasma glutamic pyruvic transaminase, $Na^+$, $K^+$, $Ca^{2+}$, $Cl^-$ and $P_i$.

   No consistent dose related effects of decamethrin were noted on these parameters.

7. Urinalysis: The following values were determined: pH, albumin, glucose, ketones, bilirubin, and occult blood (and later for nitrites and urobilinogen).

   No consistent dose-related effects were noted on any of these parameters.

Pathology

8. Organ weight (the spleen, liver, kidneys, thymus, heart, lungs, testis/ovaries, prostate/uterus, adrenals, thyroid, pituitary were weighed at 12, 18 and 24 months).

   There were no consistent dose-related effects on the above organ weights or relative organ weights.

9. Gross necropsy. (The summary tables are hard to read because of poor xeroxing.)

   No consistent dose-related effects of decamethrin were reported as being evident by gross necropsy.

10. Microscopic pathology. The protocol required that all mice in the controls (both control groups) and the high dose group and those animals which die during the course of the feeding period as well as those sacrificed at the interim sacrifice periods be examined microscopically. Thus, many of the low dose and two mid dose groups mice were not evaluated microscopically unless there was a gross observation for which follow up was required. (Their tissues were stated as being saved for future investigation). There were no dose-related increases in either nonneoplastic or neoplastic lesions reported. The tumor types reported were those which are usually associated with this strain of mouse.

11. The overall oncogenic response in mice as reported is given in the following table:

| | Males | Females |
|---|---|---|
| Control-1 | 30* | 48 |
| Control-2 | 36 | 55 |
| Low | 30 | 39 |
| Mid-1 | 25 | 34 |
| Mid-2 | 23 | 35 |
| High | 31 | 40 |

*Incidences of neoplasms only are presented; these were a total of 80 mice/sex/group. Most of the controls and the high dose test group (males and females) were given a "complete" microscopic evaluation. The low and two mid dose groups were evaluated only in response to gross necropsy lesions. Only neoplasms in the groups set to receive the treatment for 24 months is included. Individual organ discussion.

i. The liver developed a total of 26 neoplasms of these 10 were in the controls (240 mice) and 3 were in the high dose group (120 mice). Nodular hyperplasia was listed in the nonneoplastic lesions, but this type of lesion was of low net occurrence.

ii. The lung developed a total of 135 neoplasms (alveolar cell adenoma or adenocarcinoma). There were 8 incidences of the carcinoma type neoplasm. Of the 127 adenomas, there were 13 among the males and 9 among the females or 22% and 15% mice affected in the high dose test groups. The controls had as many as 28/115 (24%) and the females had 19/113 (16.8%). No oncogenic effect of deltamethrin in the lung was indicated by the data.

All other neoplasm types were of low occurrence and did not present a pattern to suggest a relationship to the test chemical.

The microscopic examination of tissues for the mice dying during the study and those sacrificed at termination was the responsibility of Dr. William W. Carlton of the American Histolabs of Silver Spring, Md. In the absence of indications to the contrary, the diagnosis of Dr. Carlton is being accepted by TB.

Conclusions: This study is CORE SUPPLEMENTARY. At the highest dose level tested decamethrin did not produce any noticeable adverse effects. Thus, the levels used have been determined by TOXICOLOGY BRANCH to be too low to define the toxic and oncogenic potential of this chemical.

003066

RU 22974 (Decamethrin) $LD_{50}$ determination and assessment of neurotoxicity in the domestic hen.

Huntingdon Research Centre, RSL/293-NT/7830/A
January 19, 1978,
EPA Acc. No. 070735, TAB C-21

Part 1. Determination of the $LD_{50}$ in hens.

Six groups of 10 hens were dosed with 800, 1200, 1600, 2000, 3000, 5000 mg/kg of RU 22974 (decamethrin) suspended in corn oil and observed for 14 days. Two additional groups were dosed with 1000 (8 hens) or 2500 (10 hens) mg/kg of decamethrin in sesame oil.

A single hen in the high dose group receiving its dose in corn oil died, all others survived. The $LD_{50}$ is considered to be >5000 mg/kg for hens. This level was considered by the testing laboratory to be the maximum practical dose level.

Four hens receiving the decamethrin in sesame oil died. One hen receiving 1000 mg/kg and 3 hens receiving 2500 mg/kg died. The $LD_{50}$ was not determined.

No detailed report on behavioral reactions resulting in the $LD_{50}$ study was presented.

Part 2. Neurotoxicity study

Seven groups of 10 hens (approx. 1 year old) were dosed as corn oil control, sesame oil control, positive control (500 mg/kg of TOCP), three dose levels of decamethrin in corn oil at 500, 1250, and 5000 mg/kg and one dose level of decamethrin in sesame oil at 1000 mg/kg. For some of the birds receiving the higher concentrations of decamethrin, it was necessary to give split doses over a period of six hours. The birds were observed for 21 days.

No signs of ataxia developed in any of the birds receiving decamethrin or solvent controls. Two of the birds dosed with decamethrin in sesame oil died. The birds dosed with TOCP developed ataxia and several were sacrificed prior to the 21 day scheduled sacrifice. Histopathology was unremarkable for the birds receiving decamethrin but signs of degeneration of fibers and myelinophages were noted in the birds receiving TOCP.

This study is CORE GUIDELINE. Decamethrin did not produce a neuropathy in hens as far as could be determined by this study.

003066

Detection of Mutagenic Potency of Decamethrin (RU 22974) Bacterial Tests

Centre de Recherches, Roussel UCLAF, Ru/tox/80.21.01/A.
January 21, 1980
EPA Acc. No. 070736, TAB C-22

1. Growth inhibition test

Strains of E. Coli (International references ATCC 27325 and ATCC 25947 (Slater strains) and NCIB 11193 (Bridges strains) were tested for mutagenic effects of decamethrin at 1250, 2500, and 5000 ug/ml. The positive controls were chloramphenicol and MNNG.

In this series of tests, decamethrin was reported as not showing mutagenic activity.

2. Ames Test

Decamethrin at concentrations of 0, 2, 10, 50, 200, 500, 1000 and 5000 ug/ml was tested with strains of Salmonella typhimurium TA 1535, 1537, 1538, 98 and 100 with and without metabolic activation. The positive controls used were N-methyl N-nitro N-nitrosoguanidine, aminoacridine and nitrofluorene. Preliminary tests indicated that decamethrin was not antimicrobial and that the compound is soluble at 100 ug/plate. At higher concentrations it is unknown how much decamethrin was available to enter the bacteria.

The study reports that decamethrin did not induce mutagenic effects in the testor strains.

RM-22974 Mutagenicity Study of Various Preparations Salmonella - microsome test

IFREB, #761153/A, date =?
EPA Acc. No. 070736, TAB 23.

Decamethrin was tested for mutagenic activity in the following strains of Salmonella typhimurium: TA1535, TA 1537, TA 1538, TA 98, and TA 100 in the presence (only) of the microsomal activation system (S9 mixture derived from rat liver). 2-aminoanthracine, 3-methylcholanthrene, benz- - pyrine, acridine orange and THIO-TEPA were used as positive controls.

The study conclusion reports that decamethrin, when tested at 0.2, 2.0, 20, 200 and 400 micrograms per plate, did not

induce mutagenic activity in these strains. At 200 and 400 ug/plate the decamethrin was present as a suspension. The positive controls were reported as inducing mutagenic activity.

This study did not attempt to determine the mutagenic effects of decamethrin in the absence of metabolic activation. It was not specifically stated how many dishes for each assay were run.

Cytogenetic Study with RM-22974 - Detection of a Mutagenic potency in mammalian cells.

Centre de Recherches Roussel - UCLAF,
#ULN-78 22II/A Nov. 22, 1978
EPA Acc. No. 070736, TAB C-24.

Part 1 - In vitro experiments with Chinese hamster cells - assessment through induction of chromosomal abnormalities and sister chromatid exchanges in the presence and absence of metabolic activation.

These studies did not give definite evidence that RU 22974 caused chromosomal abnormalities or induced sister chromatid exchanges when tested over the range of .04 to 5 mg/plate final concentration of the incubation mixture when either cremaphor oil or DMSO were used as the solvent. The use of cremaphor oil complicated the assay because of its toxicity to the cells.

These studies are not considered acceptable because only a single plate per condition was run and no positive control was included.

Part 2 - In vivo experiments in mice - Bone marrow metaphase test and micronucleus test.

Swiss mice (3 males and 3 females) were dosed with 5 or 10 mg/kg of RU22974 dissolved in sesame oil for two consecutive days. The mice were treated with colcemid solution 1 1/2 hours before sacrifice and their femurs were processed for the presence of micronuclei in 2000 polychromatic erythrocytes and for chromated aberrations in 50 cells.

No changes in the number of chromated aberrations or micronuclei in polychromated erythrocytes were noted.

This study did not include a positive control and is thus limited in its usefulness in evaluating the mutagenesis potential of RU 22974.

Part 3 - Cell-stage sensitivity. RU22974 (15 mg/kg) was given to each of 14 random bred Swiss mice and at the same time radiolabelled 6-$H^3$-thymidine was also injected. Groups of 2 mice were then sacrificed every three hours during a 24 hour period, 90 minutes before sacrifice the mice were dosed with colcemid.

Results: Several mice died from the toxicity of the RU22974. There were still no consistent dose-related trends in the distribution of aberrations to indicate an effect induced by RU 22974.

This study did not include a positive control and is thus limited in its usefulness.

003066

RU 22974-Mutagenic Study: Dominant Lethal Assay in the Male Mouse

Roussel UCLAF Res Center, # 76533/D89/A, May 17, 1977
EPA Acc. No. 070736, TAB C-25.

Five groups of 10 proven males were dosed with either sesame oil (controls), decamethrin (3 mg/kg) decamethrin (6 mg/kg) or decamethrin (15 mg/kg, this group received 1/2 of $LD_{50}$ dose and consisted of 20 mice), or 10 mg/kg Thio-TEPA (triethylenethiophosphoramide). The controls and the group receiving 3 mg/kg of decamethrin were dosed daily for seven days. Following treatment they were caged with 2 females. They were presented with 2 new females each week for 8 weeks. Coitus was ensured by the presence of a vaginal plug. The females were allowed 14 days for gestation, after which they were sacrificed and examined for antifertility effects. The males were sacrificed after the 8th week and their testicles were removed and fixed in Bouin's fluid for histopathological examination.

Results:

7 of 20 of the mice receiving 15 mg/kg decamethrin died as a result of poisoning and this group showed a decrease in mating ($\sim$ 11% when expressed as mean females mated in 8 weeks). The pregnancy rate for the controls and decamethrin treated mice was 80-100% (usually). The positive control group had a pregnancy rate of 0 at week two, but recovered at week 4.

Data on total corpora lutea, total implantations, total embryonal losses, total number of viable embryos (normal and abnormal) for all groups were determined for each of the 8 weeks. The data obtained with decamethrin treated mice essentially paralleled the control group. The positive control group (thio-TEPA) showed decreases in total corpora lutea, implantations and embryonal losses at weeks 2 and 3.

The conclusion of this study was that decamethrin does not cause dominant lethal mutations. The data presented supports this conclusion.

RU 22974-Decamethrin - Decis Technical Roussel UCLAF Sensitization Test in the guinea pig. 003066

IFREB I 709241/A. September 26, 1977. EPA Acc. No. 070734. TAB C-13.

Ten male and 10 female albino (Hartley strain) guinea pigs were prepared for the study by having their backs cleared of fur. The induction phase of this study consisted of 10 topical applications of the test substance (decis technical, batch 7B 0205) and 2 intradermal injections of Freund's complete Adjuvant. Dosings were made three times a week on at least two day intervals. The dosing consisted of application of 0.5 gm of decis under an occlusive patch for 48 hours. The patch was further covered with a impermeable plastic disc.

The challenge application was made 12 days following the last application and consisted of application of 0.5 gm of undiluted test material which was again kept in contact for 48 hours.

Evaluation of the test guinea pigs consisted of macroscopic and microscopic observation of the skin.

Results: 1. A preliminary study showed that 0.5 gm of technical Decis did not cause primary skin irritation.

2. There was no evidence generated in this study which demonstrated that Decis caused sensitization in guinea pigs.

This study in CORE MINIMUM. Decis was not a sensitizer in this study.

RU 22974 Formulation of DECIS EC 2.5 Roussel UcLaf Sensitization Test in the Guinea Pig.

IFREB #709242/A,September 1977. EPA Acc. No. 070735 Tab C-14.

The product DECIS 2.5 EC was tested in a guinea pig sensitization test by the method of Magnusson and Kligman. No evidence that the product produced signs of dermal sensitization resulted. The protocol followed was similar to the experiment indicated above using the technical decamethrin. The study is CORE MINIMUM.

Metabolism of trans and cis - Permethrin, trans and cis - Cypermethrin and Decamethrin by Microsomal Enzymes.

By Toshio Shono, Kanju Ohsawa and J. E. Casida Pesticide Chemistry and Toxicology Laboratory Dept. of Entomological Sciences University of California, Berkeley, California.

From a manuscript prepared for J. Agric and Food Chemistry 1978. EPA Acc. No. 070736 (TAB C-27)

This paper reports the procedures used in vitro and results of studying and comparing the metabolism of trans and cis permethrin and cypermethrin and of decamethrin (cis) by mouse liver. Permethrin was also studied using rat liver, housefly and cabbage looper preparations. The test results as they apply to decamethrin are discussed in this review.

Decamethrin was shown to be metabolized in the oxidase and esterase plus oxidase systems. Oxidative metabolism resulted in hydroxylation of the fragments. In particular, the cyclopropane ring was hydroxylated and several alcohol and acid derivatives of this fragment were reported. The phenoxy benzyl ring was also reported as being hydroxylated on either of the two rings and resulting metabolites were reported.

No data on tissue retention or excretion were presented. Because these data are the results of in vitro methods they are of limited value.

Oxidative, Hydrolytic and Conjugative Reactions in the Metabolism of Decamethrin in Mice.

By Luis O. Ruzo, Judith L. Engel and John E. Casida
Pesticide Chemistry and Toxicology Lab.
Dept. of Entomol. Sciences
University of California, Berkeley CA

From a manuscript prepared for J. of Agriculture and Food Chemistry 1978
EPA Acc. No. 070736 (TAB C-28).

Mice were dosed with $^{14}C$ labeled decamethrin labeled in the dibromovinyl ($^{14}C$), benzylic ($^{14}C$) and cyano ($^{14}CN$) carbon atoms and the urinary and fecal excretion and tissue retention of the isotope were determined. Attempts were also made to determine the structure of the metabolites. Several procedures were used which included both oral and Ip dosing with the labeled material in either methoxytriglycol or olive oil. Tests were also run which were designed to test the effects of piperonyl butoxide or tributyl phosphorotrithioate inhibitors of drug metabolizing oxidases and esterases.

The results demonstrated that after oral administration decamethrin was readily metabolized and excreted. The dibromovmyl labeled material was excreted most in the urine (57.3%), feces (41.7%) and only 1% remained in the tissue. The $^{14}C$ benzylic labelled material showed a lower amount of material being excreted into the urine (35.5%) and a proportionally higher amount in the feces (57.7%). After 8 days there was still 6.8% of the label derived from the CN labelled material retained in the tissue.

For both dibromyl vinyl and the benzylic labelled products, the fat tissue retained the most material (115 to 273 ppb). For the CN-labelled material the skin (778 ppb) and the stomach (1.75 ppm) retained the most material.

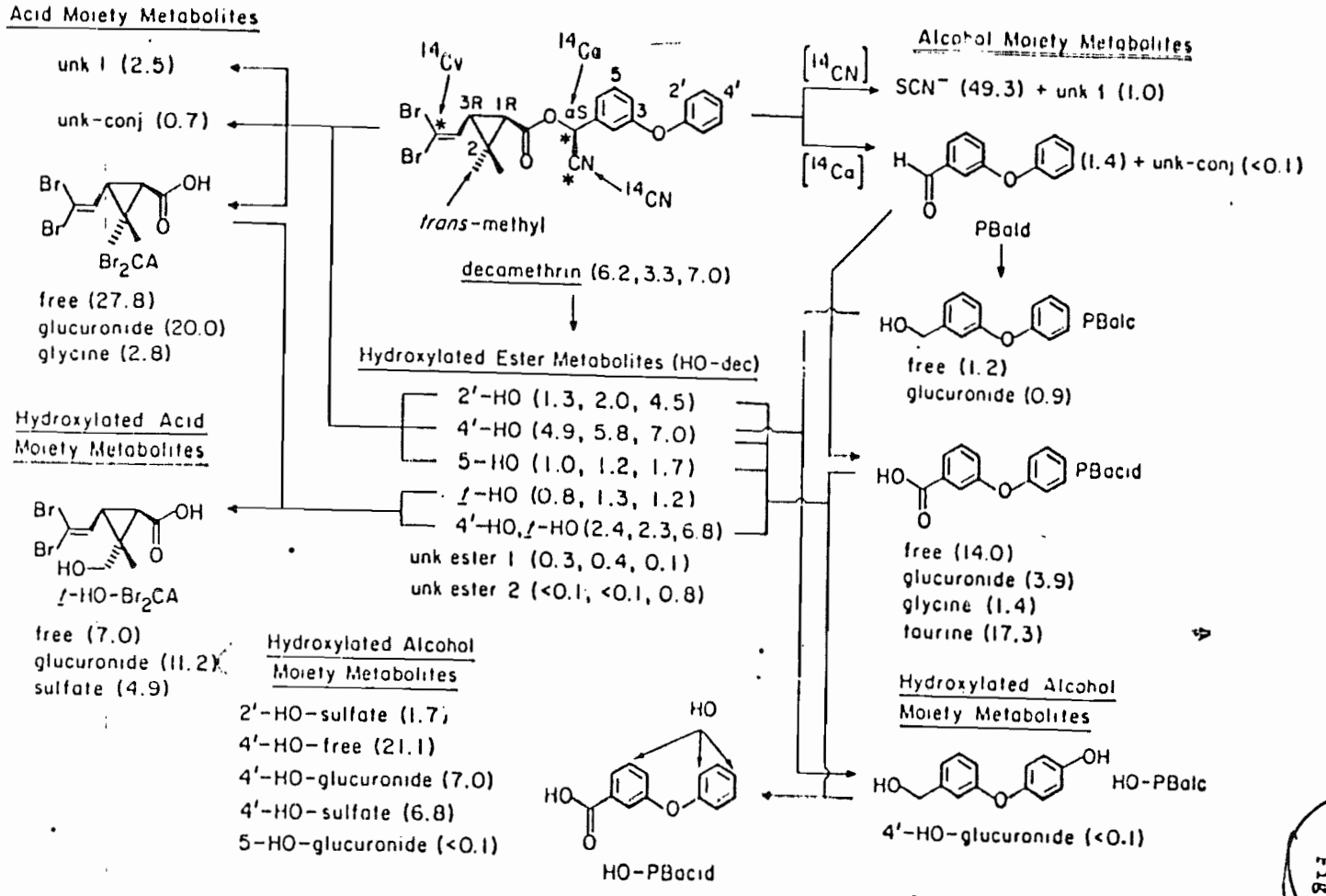
The effects of piperonyl butoxide and the organophosphate inhibitors of drug metabolizing enzymes were to decrease the rate of urinary excretion of the labelled material. Following treatment with the inhibitors, the brain levels of decamethrin reached 0.5 ppm, a level that was associated with "severe poisoning symptoms". The importance of this observation is that synergism of toxicity may result when combinations of piperonyl butoxide and/or organophosphates with decamethrin are ingested.

The accompanying figure depicts the metabolism of decamethrin in mice.

These data are considered useful in defining the metabolism of decamethrin in the mouse.

A rat metabolism study was reviewed by J. Onley (see RCB review dated July 6, 1982).

Excerpted from data submitted by the registrant J.D.O. 3/31/83




Ruzo et al.
Fig. 1

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RU 22974-DECIS Formulations: Determination of the $LD_{50}$ in the rat by oral administration

IFREB, # 770257/A, Feb. 15, 1977. Acc No. 070734 Tab C-2.

Part A. DECIS EC 2.5 (25 gm/l)

Three groups of 10 male and 10 female OFA strain (Sprague-Dawley) rats were dosed with either 0.5, 0.75, or 1 ml/kg of formulation (DECIS EC 2.5) and observed for 14 days.

An $LD_{50}$ of 0.603 ml/kg of formulation for both sexes was determined. The confidence interval was 0.499 to 0.728 by the method of Litchfield and Wilcoxon. This corresponds to 0.537 (0.445 to .649) gm/kg of test material using 0.892 as the density of the product at 20°C.

Signs of reaction to the test material included tonic convulsions, paralysis and squealing.

This study is CORE MINIMUM. No necropsy was performed. The product DECIS 2.5 EC is Toxicity Category III by the oral route.

Part B DECIS ULV (10 gm/l)

Four groups of 10 male and 10 female rats were dosed with 4.0, 6.0, 8.0, or 10.0 ml/kg of formulation (DECIS ULV) and observed for 14 days.

An $LD_{50}$ of 7.526 (6.698 to 8.456) ml of formulation/kg was determined. Signs of intoxication included lethargy, listlessness, and prostration.

This study is CORE MINIMUM. No necropsy was performed. The product DECIS ULV is Toxicity Category IV by the oral route.

Part C $LD_{50}$ of the Matric for DECIS 2.5 EC

Four groups of 10 male and 10 female rats were dosed with either 4, 6, 8, or 10 ml/kg of the matrix (solvent without deltamethrin) and observed for 14 days.

An $LD_{50}$ of 6.370 (5.595 to 7.253) ml matrix/kg was determined. The signs of intoxication included lethargy, prostration, and flaceid paralysis followed by prostration. This information verifies that the active ingredient deltamethrin is responsible for the overt signs of toxicity (convulsions) noted for the $LD_{50}$ study with DECIS 2.5 EC.

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RU 22974 [Formulation: DECIS EC 2.5 and Formulation: DECIS ULV] Acute toxicity in the rabbit by percutaneous administration.

IFREB, # 770258/A, Feb. 2, 1977. EPA Acc. No. 070734 TAB C-8.

Part A. DECIS 2.5 EC

A single group of 10 male and 10 female rabbits were prepared and dosed with 2 ml/kg of test material and observed for 14 days.

No rabbits died as a direct result of treatment (a single rabbit died due to pneumonia that is not considered to be a result of the test material). No abnormalities were noted at necropsy, bodyweight loss was described as slight.

The $LD_{50}$ is >2 ml/kg of formulation, this corresponds to 1.784 gm/kg. Because there were no deaths at this level, TB opts to assign Toxicity Category III for this product. This study is CORE MINIMUM.

Part B. DECIS ULV

Conducted similarly as above. No rabbits died, autopsy was unremarkable and body weight loss was slight.

The $LD_{50}$ is >2 ml/kg of formulation corresponding to 1.728 gm/kg of test material. Because there were no deaths at this level, TB opts to assign Toxicity Category III for this product. This study is CORE MINIMUM.

A. DECIS EC 2.5 inhalation toxicity study in rats 14 x 6 hour exposures over a period of 3 weeks 003066

Huntingdon Research Centre # RSL/319/78869/A October 19, 1978. EPA Accession No. 070735, TABC16

B. The test material was DECIS EC 2.5, a pale yellow liquid. The composition of this material was deltamethrin (2.55%), [redacted] In order to assess the toxicity of the solvent system (the matrix), the inerts alone without the deltamethrin were tested (at concentrations only slightly higher than listed as above).

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C. The test rats were CD®, obtained from the Charles River, Co. in England. They were tested as 16 per group (8 males and 8 females) and there were 5 groups as follows: control (no exposure, air only); vehicles control (solvents without detalmethrin); low (1:1000 dilution); mid (1:100 dilution); and high (1:10 dilution). The dilution ratio refers to the extent to which DECIS EC 2.5 was diluted with water prior to atmospheric generation. Exposure was for 3 weeks (14 exposures of 6 hours duration).

D. The test material was diluted as above and the test atmospheres were genereated by glass atomizers coupled to a calibrated syringe injection apparatus. The air flow rate was set at 33 l/min and the test chamber was 1 $m^3$ in volume.

E. Two samples were reportedly taken from the exposure chamber and analyzed for the atmospheric concentration of DECIS. These revealed that the levels of DECIS (as deltamethrin) were 0.03, 0.08 and 0.64 $mg/m^3$ for the ow, mid and high dose test conditions. The lowest dose level reported as at the lowerrlimit of detection of deltamethrin, and the actual amount present may have been lower. The nominal chamber concentrations were reported to be 0.08, 0.81, and 8.18 $mg/m^3$ of deltamethrin (DECIS). TB considers that the concentrations determined by analysis are a more meaningful representation of the atmospheric concentrations.

F. Particle size was determined to be 5.5 um mean aerodynamic diameter for 81-86% of the particles. A May multistage liquid impinger was used to determine the particle size.

G. Mortalities - no rats died or appeared near death as a result of exposure.

H. The reaction due to the test material (not found in the solvent control or control group) included pytalism, hyperactivity (eventual hypoactivity). Certain non-specific reactions were noted which included licking inside of the mouth, closing of eyes, scratching of the flanks, and rubbing the face. It as reported that these reactions which were reported in the solvent control groups were more intense as the concentration of deltamethrin increased.

NOEL = 0.08 $mg/m^3$

I. Body weight. Statistically significant decreases in the body weight were noted. At termination, the mid dose group males were -4% lower and the high dose group males were -7% lower. The females were also affected, the mid dose group was -4% lower and the high dose group was -8% lower.

Food consumption was noted to be lower in both the mid and high dose test groups.

NOEL = 0.08 $mg/m^3$.

For sections J, K, L below samples were taken after 11 exposures and after overnight deprivation of food and water (water was given 1 hour before sampling).

J. Urinalysis consisted of determining the volume, pH, specific gravity, protein, total reducing substance, glucose, ketones, bile pigments, urobilinogen, blood pigments and microscopy of the spun deposit.

Changes in the urine volume, pH, and specific gravity were noted in both sexes and were determined to be related to the test material. The volume was reduced to 33% for males and 46% for females and was thought to be due to renal dysfunction. The pH and specific gravity, although affected, were within normal ranges.

K. The following hematological parameters were investigated: PCV, Hb, RBC, absolute indexes (MCHC and MCV) total and differential white cell count, platelet count, thrombotest. No consistent changes due to the test material were reported.

L. The following changes in blood chemistry were noted: serum urea, glucose, total proteins, serum albumin, alkaline phosphatase, glutamic pyruric transaminase, $Na^+$, $K^+$, $Ca^{+2}$, inorganic phosphorous, cholesterol, creatimine.

Serum $Na^+$ and $K^+$ levels were statistically significantly high dose test female group. Note the effect in the $Na^+$

level was noted in the subacute inhalation study with technical deltamethrin. This may relate to the effects of the chemical in the kidney.

There were also noted some effects on total protein (decrease) and the albumin concentraiton was lower in all exposed groups.

The NOEL is 0.08 mg/$m^3$.

M. Organ Weights: The brain, pituitary, thyroids, heart, liver, spleen, adrenals, kidneys, uterus, prostrate, ovaries, testis, and epididymides were weighted.

The brain of the high dose test animals for both sexes (males +17%, females +11%) was elevated in relative weight. The mid dose levels were also higher but statistical significance was not attained.

The kidney was lower in weight for the high dose test group (males -8% and statistically significant, females -4% not significant).

The testes was +7% higher (statistically significant) for the high dose test group.

Other organs showing some signs of weight differences were the liver and spleen.

A NOEL of 0.08 mg/$m^3$ is supported. The change in brain weight is considered to be due to the lower overall body weight. The change in kidney weight may be a direct result of the test material when the large change (decrease) in urine volume and the changes in $Na^+$ and $K^+$ for this test group is taken into consideration.

N. Pathology. A comprehensive selection of 36 tissue types (plus others which may have shown some evidence of pathology) were selected and examined microscopically.

No dose related test chemical effects were noted at either macroscopic or microscopic examination.

The kidney did not display a particular type of pathology which could be related to the change in urine volume or weight change.

Conclusion. This study is CORE GUIDELINES. A NOEL of 0.08 mg/$m^3$ is supported. At higher levels (LEL = 0.64 mg/$m^3$) there were noted behavioral changes, kidney function (urine volume), organ weight differences (brain, kidneys) and decreased body weight; $Na^+$ and $K^+$ levels of the blood were also elevated.

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Note: Some of the effects noted at the level of 0.64 mg/m$^3$ were also reported in the 0.08 mg/m$^3$ dose group but the severity and magnitude were not considered sufficient to assign this level as the LEL.

Addendum: Acute toxicity data for products containing deltamethrin (DECIS 2.5 EC and DECIS ULV).

The inerts in the product to be used (DECIS 2.5 EC) have been cleared under 180.1001 c, d or e. Because this tolerance concerns imported tomatoes, no registration for the product DECIS 2.5 EC was included with this action. It should be noted that should this tolerance eventually be granted, some agreement between the importers and the EPA regarding the use of only products for which the inerts are cleared should be formalized.

Certain data for the product DECIS 2.5 EC and DECIS ULV were included in this petition although registration was not sought for these products. These studies are as follows:

| Study | Result | CORE Classification |
|---|---|---|
| DECIS 2.5 EC | | |
| Acute Oral $LD_{50}$ - rats | 0.537 (0.445 to 0.659) gm/kg - males and females (Toxicity Category III) | MINIMUM |
| Acute Dermal $LD^{50}$ - rabbits | 1.784 gm/kg or 2 ml/kg - no deaths Toxicity Category III | MINIMUM |
| Primary Dermal Irritation, rats | PII = 1.98 Toxicity Category III | MINIMUM |
| Primary Ocular Irritation, rabbits | Corneal Opacity not reversed in 21 days Toxicity Category I | GUIDELINES |
| Acute Inhalation $LC_{50}$, rats | $LC_{50}$ >5.5 ml/m$^3$ (5.5 ul/l) Toxicity Category III | MINIMUM |
| Subacute inhalation - rats (14 exposures/6 hr/ exposure) for 3 weeks | NOEL = 0.08 mg/m$^3$ (of deltamethrin) weight loss, organ weight changes, kidney effect, $Na^+$ and $K^+$ elevation in blood at 0.64 mg/m$^3$ | GUIDELINES |

| Study | Result | CORE Classification |
|---|---|---|
| Sensitization-guinea pig (Magnusson and Kligman) | Not a sensitizer | MINIMUM |
| DECIS ULV | | |
| Acute Oral $LD_{50}$ - rats | 7.526 (6.698 to 8.456) ml of formulation/kg, both sexes Toxicity Category IV | MINIMUM |
| Acute Dermal $LD_{50}$ - rabbits | >2.0 ml of formulation/ kg, both sexes or 1.728 gm/kg of test material. No deaths. Toxicity Category III | MINIMUM |
| Primary Dermal Irritation, rats | PII = 0.13 Toxicity Category IV | MINIMUM |
| Primary Ocular Irritation, rabbits | No corneal involvement Toxicity Category III | GUIDELINES |

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

003066

# Appendix I

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCE

MEMORANDUM

DATE:

TO: T.A. Gardner, PM#17
Registration Division, TS-767

SUBJECT: PP2E2663. Histopathologic evaluation of the testes from rats dosed with deltamethrin. EPA Accession #071580.

TOX Chem. No. 463B.

Background

Previous review of a 2-year rat chronic feeding/oncogenicity study (IRDC# 406-[illegible]02, submitted 5/6/80) with the synthetic pyrethroid deltamethrin indicated a possible neoplastic effect in the testis. There were 7 interstitial cell adenomas in the high dose group out of 90 animals; the first control group had 0 out of 88. A second control group, which was run concurrently, had 4 incidences of this tumor type out of 60 rats. Only 9 low dose and 13 mid dose rats were evaluated microscopically for testicular lesions.

The original report indicated that the rats from the second control group of 60 rats were prepared for histology at American Histolabs in Silver Spring, Md.; the rats from the other groups were prepared at the IRDC where the study was conducted.

Because of the possibility of an oncogenic effect, the registrant was requested at a meeting held at TB on March 22, 1983 to 1) prepare and examine microscopically all of the unexamined testes in the low and mid dose test groups; 2) have all of the slides of the testes tissues reexamined by a single pathologist; 3) provide a justification that the second control group can be used on an equal basis as the first control group; 4) provide a defense that the testis is not a target organ for an oncogenic effect of deltamethrin.

The registrant submitted on April 29, 1983 an amendment (EPA Acc. No. 071580) to the final report in response to TB's request. The report presents information that additional testes tissues from the low and mid dose test groups were prepared at a third institution (Laboratory Animal Diversified Services of Paw Paw, Michigan). All the testes tissues were then reread by a single pathologist. The results of the rereading were that two additional testicular interstitial adenomas were found: one each in the second control group and in the mid dose test level group.

The registrant's defense is that the testis is not a target organ for a neoplastic effect of deltamethrin because although the first control group had 0 incidences in 88 rats, the second control group had 5 incidences in 60 rats, meaning that the second control group response is equivalent to the high dose group response of 7 incidences in 90 rats. Both the second control group and the high dose group were within the expected range for this type of tumor in the strain of rat studied.

Recommendations

Toxicology Branch (TB) has determined that the information provided by the registrant allows the conclusion that the testis is not an oncogenic target organ for deltamethrin. This conclusion is being accepted by TB.

Detailed Considerations

1. The second control group of 60 rats which showed the development of 5 testicular interstitial adenomas is being given equal consideration as the first control group of 90 (total) rats. This second control group received the same treatment and handling as the other groups (there is no evidence that they did not) and there is no valid reason to discount this group.

2. The fact that some testis tissues were prepared for microscopy at different laboratories does not in itself invalidate the procedure or compromise the usefulness of the data. According to the amendment submitted April 29, 1983, and the letter from Mr. V. A. Dorr (May 3, 1983) essentially all of the relevant tissues in the original investigation were prepared by American Histolabs. The original report inaccurately stated the extent to which some of the tissues were prepared at the IRDC facility. The tissues from the rats dosed in the low and mid dose groups not examined in the original

investigation were prepared at the Laboratory Animal Diversified Services, Paw Paw, Michigan. Although this practice introduced a third locale for preparation of the tissues in question, this discrepancy from the desirable practice of having the same laboratory prepare the tissues is not considered consequential. According to TB staff pathologist, Dr. L. K. Kasza, the procedure used to prepare rat testes is standardized and should not vary from laboratory to laboratory. Moreover, the nature of the tumor in question should not escape detection easily.

3. The registrant provided historical control data for the incidence of testicular interstitial adenomas from 16 studies at the IRDC facility which were conducted over the years 1975 to 1979. TB eliminated two of these studies because of the low number used for the denominator (number of rats on study) and determined that the average % response was 7.56. Four of the 14 groups had no incidences (0%), two of the 14 groups had 20% or more. The high dose test group for the study with deltamethrin had 11.7% (7 incidences out of 60 rats scheduled for the full two year experiment). The second control group had 8.33% (5 out of 60). The control groups when taken together developed a total of 4.17% (5 out of 120). These data do not reach statistical significance of 0.05 using Fishers one-tailed P statistic (Toxicology Branch computer).

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